PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference TEPH 109	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/US2004/026932	International filing date *(day/month/year)* 20.08.2004	Priority date *(day/month/year)* 22.08.2003
International Patent Classification (IPC) or national classification and IPC A61B17/11, A61L27/56, A61L27/16, A61L31/04		
Applicant TEPHA, INC. et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 2 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
16.06.2005	03.11.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Schnack, A Telephone No. +49 89 2399-8149

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/026932

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-11 as originally filed

   Claims, Numbers

   1-13 filed with telefax on 18.06.2005

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/026932

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 10-13

because:

☒ the said international application, or the said claims Nos. 10-13 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-13
	No:	Claims	none
Inventive step (IS)	Yes:	Claims	none
	No:	Claims	1-13
Industrial applicability (IA)	Yes:	Claims	1-9
	No:	Claims	10-13 (see separate sheet)

2. Citations and explanations (Rule 70.7):

see separate sheet

Reference is made to the following documents:

D1: HAZARI A ET AL: "A resorbable nerve conduit as an alternative to nerve autograft in nerve gap repair" BRITISH JOURNAL OF PLASTIC SURGERY, CHURCHILL LIVINGSTONE, GB, vol. 52, 1999, pages 653-657, XP002977372 ISSN: 0007-1226

D2: C. LJUNGBERG ET AL: "Neuronal survival using a resorbable synthetic conduit as an alternative to primary nerve repair" MICROSURGERY, vol. 19, no. 6, 1999, pages 259-264, XP008040666

D3: HAZARI A ET AL: "A new resorbable wrap-around implant as an alternative nerve reapir technique" JOURNAL OF HAND SURGERY, vol. 24, no. 3, June 1999 (1999-06), pages 291-295, XP008040665

D4: WO 03/041758 A (WIBERG MIKAEL) 22 May 2003 (2003-05-22)

D5: WO 99/32536 A (METABOLIX INC) 1 July 1999 (1999-07-01)

D6: WO 01/19422 A (TEPHA INC) 22 March 2001 (2001-03-22)

D7: WO 02/07749 A (EVANS GREGORY R D ; FAN ZHEN (US); SCHMIDT MATHIAS (US); UNIV TEXAS (U) 31 January 2002 (2002-01-31)

D8: XP002311371 Retrieved from the Internet: URL:http://www.pressreleases.be/script_UK/ newsdetail.asp?ndays=m&ID=695> [retrieved on 2002-06-03]

D9: XP002311372 Retrieved from the Internet: URL:http://www.devicelink.com./mpmn/archiv e/01/10/009.html> [retrieved on 2001-10]

D10: XP002311373 Retrieved from the Internet: URL:http://www.findarticles.com/p/articles /mi_m0BPC/is_7_26/ai_89018276> [retrieved on 2002-07]

Section V

V.1. Novelty

Remarks under Article 33(3) PCT:

The presently claimed subject matter is directed to a nerve regeneration device comprising a polyhydroxyalkanoate polymer in the form of a porous conduit, wherein the polyhydroxyalkanoate polymer comprises 4-hydroxybutyrate (P4HB). Poly-4-

hydroxybutyrate is available as PHA4400, (see e.g. D6, example 5).

The documents D1-D4 appear to disclose nerve regeneration devices made from polyhydroxyalkanoate; in particular poly 3-hydroxybutyrate (P3HB). These references do not appear to deal with P4HB, for which reason novelty of the presently claimed subject matter can be acknowledged in view of these documents.

Moreover, the documents D8-D10 are press releases, which before the presently claimed priority date disclose that Tepha has submitted a Device Master File to the U.S. Food Drug Administration for its first biomaterial, a thermoplastic polyester known as PHA4400. D8-D10 further disclose that this material is intended for nerve regeneration devices, (see D8-D10, the entire documents).

However, these references do not appear to teach that the nerve regeneration device should be porous. Thus, novelty can also be acknowledged in view of these references.

V.2. Inventive step

Remarks under Article 33(3) PCT:

The difference between the presently claimed subject matter and the disclosure according to D8, D9 or D10 is that the presently claimed nerve regeneration devices is said to be *porous*, whereas D8, D9 and D10 are silent as to this technical information.

It is however considered that this difference cannot confer an inventive step to the presently claimed nerve regeneration devices because it appears to be well known in the field of nerve regeneration conduits that such conduits are advantageously porous, (see e.g. D7, page 25, line 10 - page 26, line 2 and example 2).

V.3. Industrial applicability

Remarks under Article 33(4) PCT:

The subject matter according to claims 1-10 fulfils the requirements of Article 33(4) PCT.

For the assessment of the present claims 11-14 on the question whether they are

industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

We claim:

1. A nerve regeneration device comprising a polyhydroxyalkanoate polymer in the form of a porous conduit wherein the polyhydroxyalkanoate polymer comprises 4-hydroxybutyrate.

2. The device of claim 1 wherein the polymer is poly-4-hydroxybutyrate.

3. The device of claim 1 wherein the pores of the conduit are greater than 5μm in diameter.

4. The device of claim 1 wherein the pores of the conduit are less than .500 μm in diameter.

5. The device of claim 1 wherein the conduit comprises a material selected from the group consisting of nerve cells, growth factors, and drugs.

6. A method for preparing a nerve regeneration device comprising a polyhydroxyalkanoate polymer in the form of a porous conduit wherein the polyhydroxyalkanoate comprises 4-hydroxybutyrate and wherein the device is prepared by thermally induced phase separation of the polymer in a solvent in combination with salt particles, removing the polymer solvent, and removing the salt particles.

7. The method of claim 6 comprising leaching with an alcohol followed by leaching with water or a solution comprising a surfactant.

8. The method of claim 6 for preparing the device of claim 1 wherein the device is prepared by a combination of thermally induced phase separation and poragen leaching.

9. The method of claim 7 wherein the surfactant is a polysorbate

10. A method of nerve repair or regeneration comprising providing a nerve regeneration device comprising a polyhydroxyalkanoate polymer in the form of a wrapped porous conduit wherein the polyhydroxyalkanoate comprises 4-hydroxybutyrate.

11. The method of claim 10 comprising inserting severed nerve ends into the conduit or wrapping the nerve ends with the polymer and sealing it into a conduit.

12. The method of claim 11 wherein the device is sealed by application of heat.

13. The method of claim 11 providing an axonal regeneration rate of at least 0.8 mm per day across a 10 mm sciatic nerve gap in an animal or human.